2019 Multiscale Modeling Consortium Meeting - Translation and Dissemination (March 6-7, 2019)

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MSM U01 Grant Number: 5-U01-EB021956-03

Title of Grant: Multiscale modeling of the mammalian circadian clock: The role of GABA signaling

Abstract Authors

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Abstract Text

The mammalian circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus consists of approximately 20,000 pacemaker neurons that are coupled together to produce a robust overall rhythm that drives bodily functions such as sleep patterns. The SCN represents an ideal model system for studying biological network design and behavior due to accumulating data on individual SCN neurons and their interactions. Experimental studies have shown that SCN intercellular communication is primarily mediated by two neurotransmitters: vasoactive intestinal peptide (VIP) and γ-aminobutyric acid (GABA). While VIP is well established as an essential synchronizing agent, the role of GABA remains controversial. Improved understanding of neurotransmitter mediated intercellular signaling in the SCN will have important clinical implications for prevention and treatment of circadian rhythm disruptions, including mood and sleep disorders and metabolic diseases. The goal of this project is to develop a multiscale model of the SCN and to integrate this model with targeted experiments and novel computational tools to gain improved understanding of SCN connectivity, synchronization and entrainment properties.

Context: This poster shows the progress during the 2.5 years of our project with respect to the development of integrated experimental, modeling and computational methods aimed at unraveling the effects of environmental conditions on the network topology, synchronization behavior and entrainment properties of the SCN. Motivating by these results and the importance of astrocyte modulation of GABA signaling in the SCN, we have developed the first mathematical model of SCN astrocytes. The model describes the exchange of GABA and glutamate between a single astrocyte and a neural population and captures the ability of astrocytes to adjust the neuron period. While working on the detailed biophysical model, we are also developing data driven techniques for (a) its effective reduction (using manifold learning tools like diffusion maps and using manifold learning techniques with input-output informed kernels, discovering reduced descriptors of the detailed model state) and (b) accelerating its simulation / parametric analysis through this effective reduction using equation-free techniques.

Data: Following our publication showing that astrocytes regulate daily rhythms in SCN neurons and in locomotor behavior, we are testing the hypothesis that feedback signals from SCN neurons synchronize daily rhythms in astrocytes. We have data showing that blocking neuronal firing disrupts synchrony among SCN astrocytes.We have developed a two-color system for simultaneous monitoring of astrocyte-neuron circadian interactions in vivo and in vitro. Additionally, we have data implicating GABA receptor subtypes in desynchronizing circadian rhythms in the SCN and behavior.

Evaluation: Model evaluation is ongoing. We plan to compare modeled and simulated networks of coupled neurons and astrocytes with respect to their period, synchronization and entrainment properties.

Limitations: Limited data are available to determine network connectivity between neurons and astrocytes.

Version control: Source code and text input files are maintained in locally maintained repositories that encode versioning information.

Documentation: The development of comprehensive model documentation is ongoing.

Dissemination: Current prototype models are not yet in a state suitable for broad dissemination. Simulation software will be disseminated via GitHub.

Independent reviews: Current prototype models are being independently reviewed by Dr. Stephanie Taylor (Colby College).

Test competing implementations: We are interested in developing the core models of this project using community standards to facilitate interoperability. We are investigating the use of open-source modeling infrastructure for neural network models that will allow other researchers to perform modeling and simulation studies.

Conform to standards: We intend to use community standards established for neural network models. Community standards for manifold/machine learning methods seem to be incompletely developed.